CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074412

Trade Name : CIMETIDINE HYDROCHLORIDE INJECTION

Generic Name: Cimetidine Hydrochloride Injection 300mg (base)/2ml, 2ml and 8ml multiple dose vials

Sponsor : Sanofi Pharmaceuticals, Inc.

Approval Date: March 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074412

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Pharmacology Review(s)				
Statistical Review(s)				
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Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074412

APPROVAL LETTER

ANDA 74-412

Sanofi Pharmaceuticals, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Avenue
New York, NY 10016

Dear Sir:

This is in reference to your abbreviated new drug application dated October 8, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Injection, 300 mg (base)/2 mL (2 mL Vials and 8 mL Multiple-Dose Vials).

Reference is also made to your amendments dated August 1, 1996, and January 17, and January 29, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cimetidine Hydrochloride Injection, 300 mg (base)/2 mL to be bioequivalent and therefore, therapeutically equivalent to the listed drug, Tagamet® Injection, 300 mg/2 mL of SmithKline Beecham Pharmaceuticals.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 3/28/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074412

FINAL PRINTED LABELING

NDC 0024-0267-41 8 mL Multiple-Dose Vial

Cimetidine Hydrochloride Injection

300 mg/2 mL* 150 mg per mL

*equivalent to cimetidine

FOR IM OR IV USE – DILUTE BEFORE IV USE

Caution: Federal law prohibits dispensing without prescription

SCHERING WINTHROP

Each mL contains: cimetidine hydrochloride equivalent to 150 mg of cimetidine, and 5 mg benzyl alcohol as preservative. Sodium hydroxide is added to adjust pH between 5.8 – 6.

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EXP

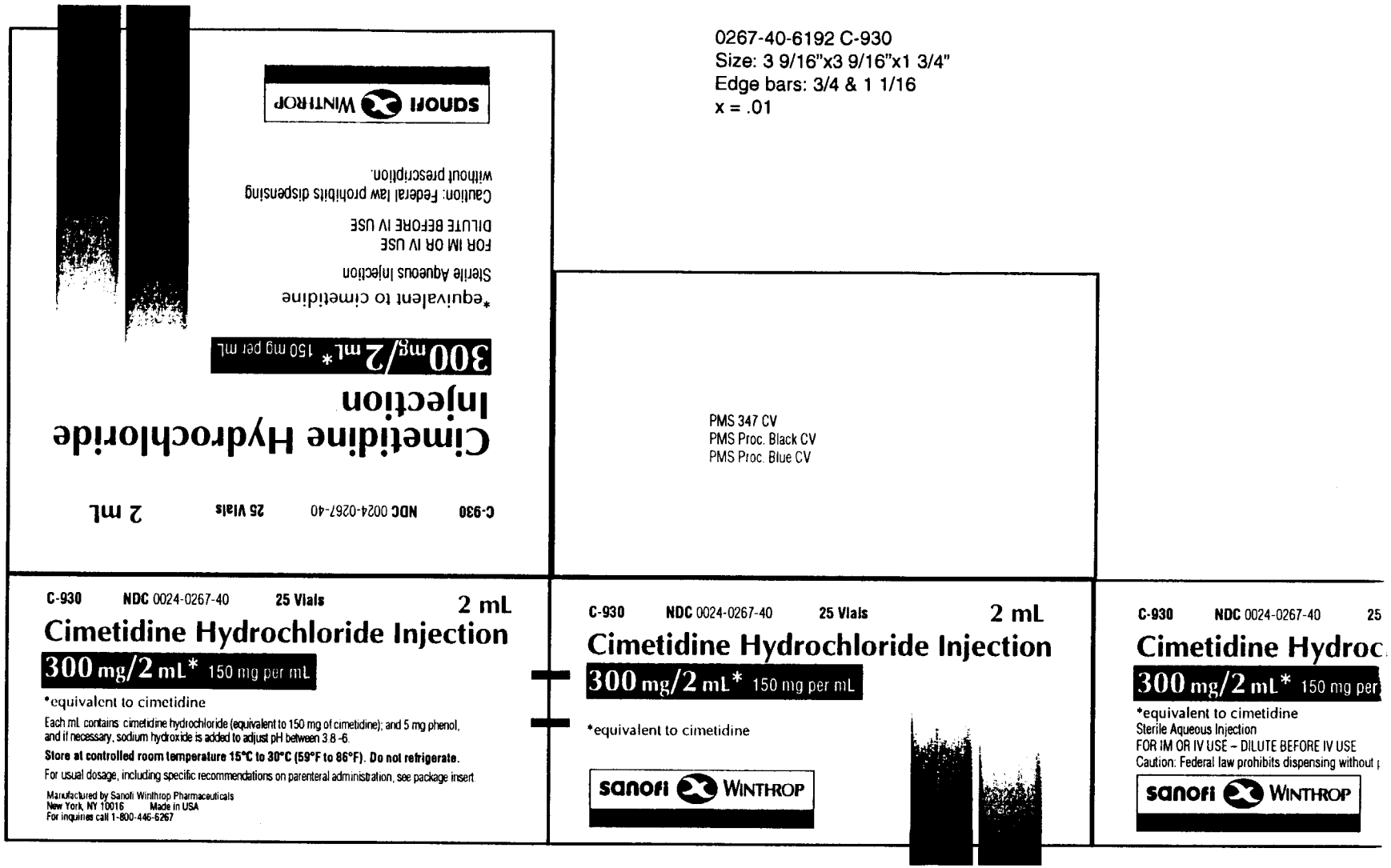
LOT

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

Dilute prior to use.

For usual dosage and pharmaceutical information, see package insert.

Made by Sanofi Winthrop Pharmaceuticals New York, NY 10016



0267-40-6192 C-930
Size: 3 9/16"x3 9/16"x1 3/4"
Edge bars: 3/4 & 1 1/16
x = .01

930 NDC 0024-0267-40 25 Vials 2 mL

imetidine Hydrochloride Injection

00 mg/2 mL* 150 mg per mL

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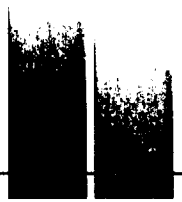
le Aqueous Injection
IM OR IV USE – DILUTE BEFORE IV USE
tion: Federal law prohibits dispensing without prescription.

sanofi WINTHROP



C-930 NDC 0024-0267-40 25 Vials 2 mL

Cimetidine Hydrochloride Injection

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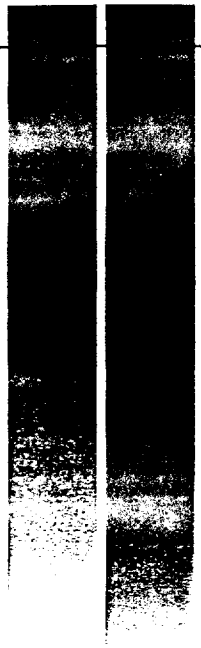
*equivalent to cimetidine

sanofi WINTHROP



SANOFI WINTHROP

Caution: Federal law prohibits dispensing without prescription.

* FOR IM OR IV USE
DILUTE BEFORE IV USE

Sterile Aqueous Injection

*equivalent to cimetidine

300 mg/2 mL* 150 mg per mL

Cimetidine Hydrochloride Injection

C-931 NDC 0024-0267-41 25 Multiple-Dose Vials 8 mL

C-931 NDC 0024-0267-41 25 Multiple-Dose Vials 8 mL

Cimetidine Hydrochloride Injection

300 mg/2 mL* 150 mg per mL

*equivalent to cimetidine

Each mL contains: cimetidine hydrochloride (equivalent to 150 mg of cimetidine); and 5 mg phenol, and if necessary, sodium hydroxide is added to adjust pH between 3.8- 6.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F). Do not refrigerate.

For usual dosage, including specific recommendations on parenteral administration, see package insert.

Manufactured by Sanofi Winthrop Pharmaceuticals
New York, New York 10016 Made in USA
For inquiries call 1-800-446-6267

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Size"
Edge
x = .0

PMS 347
PMS Proc
PMS Proc

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0267-41-6192 C-931
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x = .01

PMS 347 CV
PMS Proc. Black CV
PMS Proc. Blue CV

C-931 NDC 0024-0267-41 25 Multiple-Dose Vials 8 mL

Cimetidine Hydrochloride Injection

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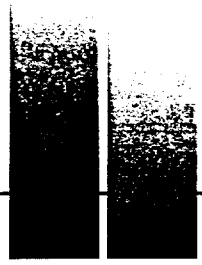
sanofi WINTHROP



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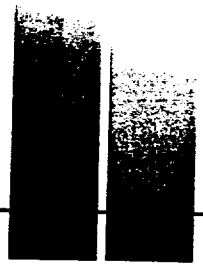

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*equivalent to cimetidine

sanofi WINTHROP

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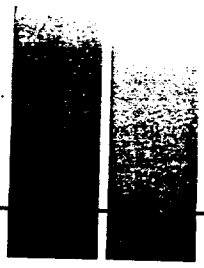

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Cimetidine Hydrochloride Injection

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*equivalent to cimetidine

sanofi WINTHROP

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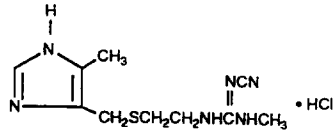
CIMETIDINE HYDROCHLORIDE INJECTION

DESCRIPTION

Cimetidine is a histamine H_2- receptor antagonist. Chemically it is *N* "-cyano-*N*'-methyl-*N* -[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]-ethyl], guanidine. The molecular formula for cimetidine hydrochloride is $C_{10}H_{16}N_6S \cdot HCl$; and the molecular weight is 288.80. The structural formula of cimetidine hydrochloride is:



Cimetidine hydrochloride contains an imidazole ring, and is chemically related to histamine. Cimetidine hydrochloride has a bitter taste and characteristic odor.

Solubility Characteristics

Cimetidine hydrochloride is freely soluble in water, soluble in alcohol, very slightly soluble in chloroform and practically insoluble in ether.

Cimetidine hydrochloride injection is a sterile aqueous solution intended for IM/IV use. Each mL contains cimetidine hydrochloride equivalent to 150 mg of cimetidine; 5 mg phenol, and if necessary, sodium hydroxide is added to adjust pH between 3.8-6.

CLINICAL PHARMACOLOGY

Cimetidine competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus is a histamine H_2- receptor antagonist.

Cimetidine is not an anticholinergic agent. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Antisecretory Activity

1) Acid Secretion: *Nocturnal:* Cimetidine 800 mg orally at bedtime reduces mean hourly H+ activity by greater than 85% over an eight-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. Cimetidine 1600 mg orally h.s. produces 100% inhibition of mean hourly H+ activity over an eight-hour period in duodenal ulcer patients, but also reduces H+ activity by 35% for an additional five hours into the following morning. Cimetidine 400 mg b.i.d. and 300 mg q.i.d. decrease nocturnal acid secretion in a dose-related manner, i.e., 47% to 83% over a six- to eight-hour period and 54% over a nine-hour period, respectively.

Food Stimulated: During the first hour after a standard experimental meal, oral cimetidine 300 mg inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours cimetidine inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg breakfast dose of cimetidine continued for at least four hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg dose of cimetidine given with lunch.

In another study, cimetidine 300 mg given with the meal increased gastric pH as compared with placebo.

	Mean Gastric pH	
	Cimetidine	Placebo
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

24-Hour Mean H+ Activity: Cimetidine 800 mg h.s., 400 mg b.i.d. and 300 mg q.i.d. all provide a similar, moderate (less than 60%) level of 24-Hour acid suppression. However, the 800 mg h.s. regimen exerts its entire effect on nocturnal acid, and does not affect daytime gastric physiology.

Chemically Stimulated: Oral cimetidine significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine and insulin as follows:

Stimulant	Stimulant Dose	Cimetidine	%Inhibition
Betazole	1.5 mg/kg (sc)	300 mg (po)	85% at 2 1/2 hours
Pentagastrin	6 mcg/kg/hr (iv)	100 mg/hr (iv)	60% at 1 hour
Caffeine	5 mg/kg/hr (iv)	300 mg (po)	100% at 1 hour
Insulin	0.03 units/kg/hr (v)	100 mg/hr (iv)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45% to 75% and the inhibition of volume ranged from 30% to 65%.

Parenteral administration also significantly inhibits gastric acid secretion. In a crossover study involving patients with active or healed duodenal or gastric ulcers, either continuous I.V. infusion of cimetidine 37.5 mg/hour (900 mg/day) or intermittent injection of cimetidine 300 mg q6h (1200 mg/day) maintained gastric pH above 4.0 for more than 50% of the time under steady-state conditions.

2) **Pepsin:** Oral cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice.

3) **Intrinsic Factor:** Intrinsic factor secretion was studied with betazole as a stimulant. Oral cimetidine 300 mg inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

Other

Lower Esophageal Sphincter Pressure and Gastric Emptying

Cimetidine has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

Pharmacokinetics

The half-life of cimetidine is approximately 2 hours. Both oral and parenteral (I.V. or

2 hours		
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Other

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Pharmacokinetics

The half-life of cimetidine is approximately 2 hours. Both oral and parenteral (I.V. or I.M.) administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours following a dose of 300 mg.

Steady-state blood concentrations of cimetidine with continuous infusion of cimetidine hydrochloride are determined by the infusion rate and clearance of the drug in the individual patient. In a study of peptic ulcer patients with normal renal function, an infusion rate of 37.5 mg/hour produced average steady-state plasma cimetidine concentrations of about 0.9 mcg/mL. Blood levels with other infusion rates will vary in direct proportion to the infusion rate.

The principal route of excretion of cimetidine is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following I.V. or I.M. administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

Clinical Trials

Duodenal Ulcer

Cimetidine has been shown to be effective in the treatment of active duodenal ulcer and, at reduced dosage, in maintenance therapy following healing of active ulcers.

Active Duodenal Ulcer: Cimetidine accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with oral cimetidine are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates
With Various Oral Cimetidine Dosage Regimens*

REGIMEN	300 mg q.i.d.	400 mg b.i.d.	800 mg h.s.	1600 mg h.s.
Week 4	68%	73%	80%	86%
Week 6	80%	80%	89%	—
Week 8	—	92%	94%	—

* Averages from controlled clinical trials.

A U.S., double-blind, placebo-controlled, dose-ranging study demonstrated that all once-daily at bedtime (h.s.) cimetidine regimens were superior to placebo in ulcer healing and that cimetidine 800 mg h.s. healed 75% of patients at four weeks. The healing rate with 800 mg h.s. was significantly superior to 400 mg h.s. (66%) and not significantly different from 1600 mg h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving cimetidine 800 mg h.s. experienced nocturnal pain relief after one day. Relief from daytime pain was reported in approximately 70% of patients after two days. As with ulcer healing, the 800 mg h.s. dose was superior to 400 mg h.s. and not different from 1600 mg h.s.

In foreign, double-blind studies with cimetidine 800 mg h.s., 79% to 85% of patients were healed at four weeks.

While short-term treatment with cimetidine can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after cimetidine has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on cimetidine than for patients healed on other forms of therapy; however, the cimetidine-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer: Treatment with a reduced dose of cimetidine has been proven effective as maintenance therapy following healing of active duodenal ulcers.

In numerous placebo-controlled studies conducted worldwide, the percent of patients with observed ulcers at the end of one year's therapy with cimetidine 400 mg h.s. was significantly lower (10% to 45%) than in patients receiving placebo (44% to 70%). Thus, from 55% to 90% of patients were maintained free of observed ulcers at the end of one year with cimetidine 400 mg h.s.

Factors such as smoking, duration and severity of disease, gender, and genetic traits may contribute to variations in actual percentages.

Trials of other anti-ulcer therapy, whether placebo-controlled, positive-controlled or open, have demonstrated a range of results similar to that seen with cimetidine.

Active Benign Gastric Ulcer

Cimetidine has been shown to be effective in the short-term treatment of active benign gastric ulcer.

In a multicenter, double-blind U.S. study, patients with endoscopically confirmed benign gastric ulcer were treated with cimetidine 300 mg four times a day or with placebo for six weeks. Patients were limited to those with ulcers ranging from 0.5 to 2.5 cm in size. Endoscopically confirmed healing at six weeks was seen in significantly* more cimetidine-treated patients than in patients receiving placebo, as shown below:

	Cimetidine	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%)*	30/67 (45%)

*p<0.05

In a similar multicenter U.S. study of the 800 mg h.s. oral regimen, the endoscopically confirmed healing rates were:

	Cimetidine	Placebo
total at week 6	63/83 (76%)*	44/80 (55%)

*p=0.005

Similarly, in worldwide double-blind clinical studies, endoscopically evaluated benign gastric ulcer healing rates were consistently higher with cimetidine than with placebo.

Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients

A double-blind, placebo-controlled randomized study of continuous infusion cimetidine was performed in 131 critically ill patients (mean APACHE II score =15.99) to compare the incidence of upper gastrointestinal bleeding, manifested as hematemesis or bright red blood which did not clear after adjustment of the nasogastric tube and a 5 to 10 minute lavage, persistent Gastroccult® positive coffee grounds for 8 consecutive hours which did not clear with 100 cc lavage and/or which were accompanied by a drop in hematocrit of 5 percentage points, or melena, with an endoscopically documented upper gastrointestinal source of bleed. 14% (9/65) of patients treated with cimetidine continuous infusion developed bleeding compared to 33% (22/66) of the placebo group. Coffee grounds was the manifestation of bleeding that accounted for the difference between groups. Another randomized, double-blind placebo-controlled study confirmed these results for an end point of upper gastrointestinal bleeding with a confirmed upper gastrointestinal source noted on endoscopy, and by post hoc analyses of bleeding episodes between groups.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Cimetidine significantly inhibited gastric acid secretion and reduced occurrence of diarrhea, anorexia and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas. Use of cimetidine was also followed by healing of intractable ulcers.

INDICATIONS AND USAGE

Cimetidine hydrochloride injection is indicated in:

(1) **Short -Term Treatment of Active Duodenal Ulcer.** Most patients heal within 4 weeks and there is rarely reason to use cimetidine at full dosage for longer than 6 to 8 weeks (see DOSAGE AND ADMINISTRATION - Duodenal Ulcer). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of oral cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of oral cimetidine.

(2) **Maintenance Therapy for Duodenal Ulcer Patients at Reduced Dosage After Healing of Active Ulcer.** Patients have been maintained on continued treatment with cimetidine 400 mg h.s. for periods of up to five years.

(3) **Short -Term Treatment of Active Benign Gastric Ulcer.** There is no information concerning usefulness of treatment periods of longer than 8 weeks.

(4) **Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients.**

(5) **The Treatment of Pathological Hypersecretory conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).**

CONTRAINDICATIONS

Cimetidine is contraindicated for patients known to have hypersensitivity to the product.

PRECAUTIONS

General: Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of cimetidine hydrochloride injection by intravenous bolus.

Symptomatic response to cimetidine therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see ADVERSE REACTIONS) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. As
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developed bleeding compared to 33% (22/66) of the placebo group. Coffee grounds was the manifestation of bleeding that accounted for the difference between groups. Another randomized, double-blind placebo-controlled study confirmed these results for an end point of upper gastrointestinal bleeding with a confirmed upper gastrointestinal source noted on endoscopy, and by post hoc analyses of bleeding episodes between groups.

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Reversible confusional states (see ADVERSE REACTIONS) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal.

Drug Interactions: Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either cimetidine 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline extended-release tablets demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered cimetidine to maintain optimum therapeutic blood levels.

Alteration of pH may affect absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other drugs affected by the concomitant administration of cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 8 to 48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Cimetidine has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 8 to 48 times the full therapeutic dose of cimetidine, as compared with controls.

The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, cimetidine has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or *in vitro* fertilizing capacity.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cimetidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

Pediatric Use: Clinical experience in pediatric patients is limited. Therefore, cimetidine therapy cannot be recommended for pediatric patients under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20 to 40 mg/kg per day have been used.

Immunocompromised Patients: In immunocompromised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

ADVERSE REACTIONS

Adverse effects reported in patients taking cimetidine are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

Gastrointestinal: Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS: Headaches, ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2,225 patients taking 800 mg/day and 2.3% of 1,897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2 to 3 days of initiation of cimetidine therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for one month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving cimetidine, particularly in high doses, for at least 12 months (range 12 to 79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Hematologic: Decreased white blood cell counts in cimetidine-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H_2- receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary: Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare reports of cholestatic or mixed cholestatic-hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in the occasional liver injury with other H_2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving cimetidine.

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity: Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal: Small, possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion, are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular: Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2- receptor antagonists.

Musculoskeletal: There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with preexisting arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in cimetidine dosage. Rare cases of polymyositis have been reported, but no causal relationship has been established.

Integumental: Mild rash and, very rarely, cases of severe generalized skin reactions including Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

OVERDOSAGE

Studies in animals indicate that toxic doses are associated with respiratory failure and tachycardia which may be controlled by assisted respiration and the administration of a beta-blocker.

Reported acute ingestions of up to 20 grams have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and cimetidine 4800 mg intravenously over a 24 hour period experienced mental deterioration with reversal on

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There have been two deaths in adults who have been reported to have ingested over 40 g orally on a single occasion.

DOSAGE AND ADMINISTRATION

Parenteral Administration

In hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, cimetidine may be administered parenterally.

Recommendations for Parenteral Administration

Intramuscular Injection: 300 mg every 6 to 8 hours (no dilution necessary). Transient pain at the site of injection has been reported.

Intravenous Injection: 300 mg every 6 to 8 hours. In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of a 300 mg dose, but should not exceed 2400 mg per day. Dilute cimetidine hydrochloride injection, 300 mg, in Sodium Chloride Injection (0.9%) or another compatible I.V. solution (see Stability of Cimetidine Hydrochloride Injection) to a total volume of 20 mL and inject over a period of not less than 5 minutes (see PRECAUTIONS).

Intermittent Intravenous Infusion: 300 mg every 6 to 8 hours, infused over 15 to 20 minutes. In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of a 300 mg dose, but should not exceed 2400 mg per day.

Dilute cimetidine hydrochloride injection, 300 mg, in at least 50 mL of Dextrose Injection 5%, or another compatible I.V. solution (see Stability of Cimetidine Hydrochloride injection).

Continuous Intravenous Infusion: 37.5 mg/hour (900 mg/day). For patients requiring a more rapid elevation of gastric pH, continuous infusion may be preceded by a 150 mg loading dose administered by I.V. infusion as described above. Dilute 900 mg cimetidine hydrochloride injection in a compatible I.V. fluid (see Stability of Cimetidine Hydrochloride Injection) for constant rate infusion over a 24-hour period. Note: Cimetidine may be diluted in 100 to 1000 mL; however, a volumetric pump is recommended if the volume for 24-hour infusion is less than 250 mL. In one study in patients with pathological hypersecretory states, the mean infused dose of cimetidine was 160 mg/hour with a range of 40 to 600 mg/hour.

These doses maintained the intragastric acid secretory rate at 10 mEq/hour or less. The infusion rate should be adjusted to individual patient requirements.

Stability of Cimetidine Hydrochloride Injection

When added to or diluted with most commonly used intravenous solutions, e.g., Sodium Chloride Injection (0.9%), Dextrose Injection (5% or 10%), Lactated Ringer's Injection, Sodium Bicarbonate Injection 5%, cimetidine hydrochloride injection should

not be used after more than 48 hours of storage at room temperature.

NOTE: The products accompanying this insert are for IM/IV use only. Much of the following relates to the use of oral cimetidine and is for informational purposes only. See Parenteral Administration (above) for specific dosing recommendations.

Duodenal Ulcer

Active Duodenal Ulcer: Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing (see CLINICAL PHARMACOLOGY — Acid Secretion). This is supported by recent clinical trials (see Clinical Trials — Active Duodenal Ulcer). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime oral dosage regimen (h.s.).

In a U.S dose-ranging study of 400 mg h.s., 800 mg h.s. and 1600 mg h.s., a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg h.s. is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 mg h.s. and 1600 mg h.s. being small), maximal pain relief, a decreased potential for drug interactions (see PRECAUTIONS — Drug Interactions) and maximal patient convenience. Patients unhealed at four weeks, or those with persistent symptoms, have been shown to benefit from two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are also heavy smokers (i.e., smoke one pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with cimetidine 1600 mg at bedtime. While early pain relief with either 800 mg h.s. or 1600 mg h.s. is equivalent in all patients, 1600 mg h.s. provides an appropriate alternative when it is important to ensure healing within four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with cimetidine 800 mg h.s.

Other cimetidine regimens in the U.S. which have been shown to be effective are: 300 mg four times daily, with meals and at bedtime, the original regimen with which U.S. physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (see Clinical Trials — *Active Duodenal Ulcer*).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of *oral* cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of cimetidine.

While healing with cimetidine often occurs during the first week or two, treatment should be continued for 4 to 6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance Therapy for Duodenal Ulcer: In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

Active Benign Gastric Ulcer

The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 800 mg h.s., or 300 mg four times a day with meals and at bedtime. Controlled clinical studies were limited to six weeks of treatment (see **Clinical Trials**). 800 mg h.s. is the preferred regimen for most patients based upon convenience and reduced potential for drug interactions. Symptomatic response to cimetidine does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

Prevention of Upper Gastrointestinal Bleeding

The recommended adult dosing regimen is continuous IV infusion of 50 mg/hour. Patients with creatinine clearance less than 30 cc/min. should receive half the recommended dose. Treatment beyond 7 days has not been studied.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 300 mg four times a day with meals and at bedtime. In some patients it may be necessary to administer higher doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg per day and should continue as long as clinically indicated.

Dosage Adjustment for Patients with Impaired Renal Function

Patients with severely impaired renal function have been treated with cimetidine. However, such usage has been very limited. On the basis of this experience the recommended dosage is 300 mg every 12 hours orally or by intravenous injection. Should the patient's condition require, the frequency of dosing may be increased to every 8 hours or even further with caution. In severe renal failure, accumulation may occur and the lowest frequency of dosing compatible with an adequate patient response should be used. When liver impairment is also present, further reductions in dosage may be necessary. Hemodialysis reduces the level of circulating cimetidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Patients with creatinine clearance less than 30 cc/min. who are being treated for prevention of upper gastrointestinal bleeding should receive half the recommended dose.

All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Cimetidine Hydrochloride Injection is available as:

300 mg/2 mL (150 mg/mL) (2 mL vial), box of 25 (NDC 0024-0267-40).
300 mg/2 mL (150 mg/mL) (8 mL multiple-dose vial), box of 25 (NDC 0024-0267-41).

Store at controlled room temperature 15° C to 30° C (59° F to 86° F). Do not refrigerate.

Caution: Federal law prohibits dispensing without prescription.

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sanofi WINTHROP

Manufactured by Sanofi Winthrop Pharmaceuticals
New York, NY 10016

Made in USA

Revised January 1997
CSW-5A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074412

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. **4**

2. ANDA # **74-412**

3. NAME AND ADDRESS OF APPLICANT
Sanofi Pharmaceuticals, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Ave.
New York, NY 10016

4. LEGAL BASES FOR ANDA SUBMISSION
Generic version of Smith-Kline Beechman's **TAGAMET®** (NDA 17-939). Patent certification and exclusivity statement are provided (pp. 013-014).

U.S. Patent No. 4,024,271 expired May 17, 1994.

Final approval date is October 31, 1985

5. SUPPLEMENT(s) N/A

6. NAME OF DRUG
Cimetidine Hydrochloride Injection

7. PROPRIETARY NAME

8. SUPPLEMENT(s) PROVIDE(s) FOR: Original ANDA

9. AMENDMENTS AND OTHER DATES:

FIRM		**FDA**	
Orig. submission	10/08/93	Refuse to file	10/29/93
		CSO review	10/20/93
Amendment (major)	12/03/93	Acknowledge letter	12/15/93
		Bio review	01/26/94
		Label review #1	05/11/94
		Deficiency letter	06/22/94
		Micro review #1	07/12/94
		Micro deficiency	08/02/94
New correspondence	09/30/94		
Amendment (micro)	10/07/94		
Amendment (major)	11/11/94	Label review #2	11/30/94
		Micro review #2	01/11/95
		Deficiency letter	08/31/95
Amendment (major)	08/01/96	Label review #3	12/04/96
New correspondence	01/17/97		
Amendment (minor)	01/29/97	Label review #4	2/21/97

This review covers amendment dated 1/29/97.

10. PROPOSED INDICATIONS FOR USE

H-2 Receptor Histamine Antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

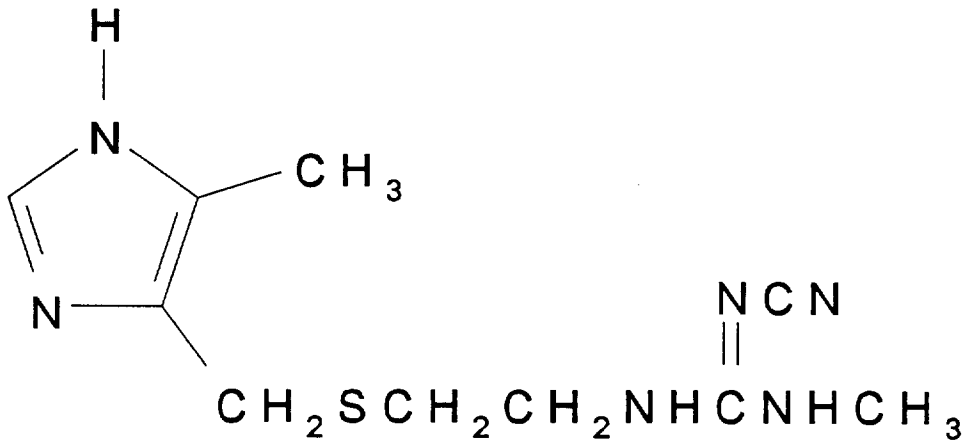
(b)4 - Confidential Business

13. DOSAGE FORM
Injection (IM, IV) Vials

14. STRENGTH
150 mg base/mL

15. CHEMICAL NAME AND STRUCTURE

Cimetidine USP
$C_{10}H_{16}N_6S$; M.W. = 252.34



2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]-ethyl]guanidine. CAS [51481-61-9]

Drug substance and drug product <u>are not</u> official USP items.

16. RECORDS AND REPORTS N/A

17. COMMENTS
a. Labeling found satisfactory, dated 2/21/97.
b. Exclusionary period ends on Nov. 13, 1994.
c. Microbiology review found satisfactory, dated 1/11/95.
d. Methods validation for drug substance and drug product found satisfactory and can be used for regulatory purposes, dated 8/14/94.
e. DMF (b)(4) found satisfactory, dated 10/31/96.
f. Bio found satisfactory, dated 1/26/94.
g. Establishment Evaluation Request **pending.**

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVE

19. REVIEWER: Raymond Brown

DATE COMPLETED: February 27, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074412

BIOEQUIVALENCE REVIEW(S)

JAN 26 1994

Cimetidine Hydrochloride
150 mg/mL Injectable
[redacted]
Reviewer: S.P. Shrivastava, Ph.D.
WP #74412W.O93

Sterling Winthrop Inc.
New York, NY-10016
Submission Date:
October 8, 1993

REVIEW OF A BIO-WAIVER REQUEST

I.INTRODUCTION: Cimetidine is a histamine hydrogen receptor antagonist. Chemically it is N"-cyano-N-methyl-N'-[2-[[(5-methyl-1H-imidazole-4-yl)methyl]thio]-ethyl]-guanidine. The molecular formula is $C_{10}H_{16}N_6S.HCl$, which corresponds to a molecular weight of 288.80. The compound is freely soluble in water and alcohol, very slightly soluble in chloroform, and is practically insoluble in ether.

The oral availability of cimetidine is about 62±6%. The absorption is rapid with Cmax observable within two hours. The drug is primarily eliminated by urinary excretion, the excretion being 62±20%. Plasma binding is minimal around 20%. Clearance is about 8.3±2.0 mL/min/kg; volume of distribution is 1.0±0.2 L/kg; and the half-life is about 2 hours.

II.CURRENT APPLICATION: The current application consists of a biostudy waiver request for the firm's cimetidine hydrochloride 150 mg/mL injectable (2 mL and 8 mL vials), based on the identical content and composition, and similarity of the dosage form and administration route compared to the approved innovator product Tagamet[R] (cimetidine hydrochloride) 300 mg/2 mL (2 mL single-dose, and 8 mL multi-dose vials), manufactured by SmithKline Beecham Pharmaceuticals.

III.COMPOSITION: Following is the composition of the test and the reference formulations. The quantities are expressed as per mL:

Ingredients	Test	Reference
Cimetidine Hydrochloride	172 mg*	172 mg
Phenol USP	5.00 mg	5.00 mg
Water for Injection	1.00 mL	1.00 mL
0.1 N NaOH q.s. pH	[redacted](b)4 - Confidential[redacted]	
Nitrogen NF		

* = Equivalent to 150 mg cimetidine base.

In the above formulation, cimetidine is the active ingredient and phenol is the preservative. The test and proposed production batch sizes are [redacted](b)4 -[redacted]

IV.COMMENTS

1. The ingredients of the test and reference formulations are qualitatively and quantitatively identical.

2. The route of administration is identical for both formulations.

3. The fill volume, osmolality and pH are also identical.

V.RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Sterling Winthrop Inc. demonstrates that cimetidine hydrochloride, 172 mg/mL equivalent to 150 mg/mL cimetidine base (supplied as 2 mL and 8 mL vials), falls under 21 CFR (1993) Section 320.22 (b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for 150 mg/mL (2mL and 8 mL injectable) of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Tagamet^{R}, 300 mg/2 mL, injectable in 2 mL and 8 mL vials, manufactured by SmithKline Beecham Pharmaceuticals.

/S/

S.P. Shrivastava, Ph.D.
Division of Bioequivalence,
Review Branch II.

RD INITIALED BY RNPatnaik
FT INITIALED BY RNPatnaik /S/ Date: 1/26/94

cc: ANDA 74-412 (original, duplicate), HFD-630, HFD-600 (Hare), HFC-130 (JAllen), HFD-655 (Shrivastava, Patnaik), Division File, Drug File.

SPS/sps/01-18-94/WP #74412W.O93